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Genetic and Perinatal Risk Factors for Asthma Onset and Severity: A Review and Theoretical Analysis

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Abbreviations: AR, adrenergic receptor; Ig, immunoglobulin; IL, interleukin; TNF, tumor necrosis factor.

INTRODUCTION

Asthma is a major chronic disease, and several studies indicate that it is on the rise worldwide (1). A recent report (2) from the Centers for Disease Control and Prevention estimated that the prevalence of self-reported asthma in the United States rose 75 percent from 1980 to 1994, with 17.3 million asthmatics in 1998 (3). In 2000, asthma accounted for more than 11.2 million medical visits, including 1.8 million to emergency rooms (4, 5). Asthma is characterized by lung inflammation, reversible airflow obstruction, and enhanced airway responsiveness to a variety of environmental stimuli and is a phenotypically heterogeneous disorder with variable disease expression.

Asthma has a considerably greater impact on Hispanics and African Americans than on Whites in the United States (2, 6–12). Compared with Whites, African-American children have higher (1.1–1.7 times) asthma prevalence rates (2, 13–18), 2–3.5 times the hospital admission rate for asthma (2, 19–23), and approximately 2–5 times the asthma mortality rate (2, 22, 24–26). Point prevalence asthma rates of 11.2 percent and cumulative prevalence rates (ever had asthma) of 20.1 percent are reported for Puerto Rican children, the highest for any ethnic group in the United States (12, 27).

Asthma increasingly has been diagnosed in young children, starting in the 1970s (28) and continuing through the last two decades (29–31), but precise rates cannot be readily obtained because of the difficulty in diagnosing asthma in very young children (32). Wheezing is often used as a surrogate measure but is unreliable; in a Tucson, Arizona, cohort, by age 3 years, 19.9 percent of the children had at least one lower respiratory tract illness with wheeze but were no longer wheezing at age 6 years, 15.0 percent did not wheeze before age 3 years but did so at age 6 years, and 49.5 percent wheezed by age 6 years (33). Wheeze has been reported in the winter of the first year of life in 33 percent of infants (34) and to occur for 30 or more days in one third of infants who do wheeze (35). The difficulty in diagnosing childhood asthma has led to suggestions that the increase is in milder symptoms only and that some children may be treated inappropriately (29, 36).

Despite a considerable literature on risk factors for asthma onset and severity in children, very little is known about possible intrauterine influences, particularly how these factors interact with the genotype to sensitize the fetus to allergen exposure in infancy. There have been several recent reviews of candidate genes, but they often have excluded consideration of those environmental risk factors likely to play a role in gene-environment interactions.

In this review, we first discuss some of the major candidate genes currently thought to play a role in affecting susceptibility to allergen sensitization, inflammation and tissue damage, and asthma symptoms and bronchial hyperreactivity. We then consider perinatal risk factors, including intrauterine exposure and influence of the fetal environment. We summarize the literature regarding lactation and diet, early neonatal exposure, and environmental risk factors. Finally, we propose a model that describes the possible interplay of these factors in a plausible temporal sequence.

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GENETIC FACTORS

Although environmental factors are clearly important determinants of asthma, numerous studies have revealed that asthma has a strong genetic component but does not follow monogenic patterns of inheritance (37–39). For a long time, asthma has been known to cluster in families, and family studies were the first to suggest that the disease was genetically inherited. More recent family studies found, for example, a 60 percent increased risk of atopy when both parents were affected (40), and the odds of asthma in a child increased from 3 when one parent was affected to 6 when both were (41). Maternal asthma appears to be more influential than paternal asthma (41, 42), particularly in children less than age 5 years (41). While family studies point to the likely importance of a genetic etiology, these studies do not definitively delineate genetic from environmental risks because of shared environments in families.

Twin studies were among the earliest to demonstrate the importance of genetic factors in the etiology of asthma. One of these, conducted in Sweden (43), reported concordance rates for self-reported asthma of 19.0 percent in monozygotic and 4.8 percent in dizygotic twins. There have been many replications of this finding. Current twin studies confirm the importance of both genetic and environmental factors by comparing the concordance rates in monozygotic versus dizygotic twins from the same population, who are at increased risk of asthma because of parental atopy (44). In Finnish Twin Studies, 87 percent of the variation in susceptibility to asthma was owed to genetic factors in families with at least one asthmatic parent. Among families in which neither parent was asthmatic, the development of asthma was explained entirely by environmental risk factors (45, 46). Twin studies permit analysis of environmental risk factors, independent of genetic factors, without necessarily knowing the specific genes involved (47–50).

The strategy for identifying candidate genes offers opportunities to further specify persons at increased risk for susceptibility to allergic sensitization (atopy), inflammation, bronchial hyperreactivity, and severity of asthma symptoms. Confirming the importance of candidate asthma genes will enable development of new diagnostic and therapeutic tools and of prevention and allergen avoidance strategies. Identification of candidate genes for asthma will also permit more precise elucidation of environmental risk factors operating at different stages of asthma development. Nonetheless, careful analysis and interpretation of these studies is required. Three explanations are possible for an association between a candidate gene and disease (51): 1) the candidate allele is the relevant mutation in the disease gene; 2) the allele is positioned very close to the disease gene (linkage disequilibrium); or 3) the association is due to confounding by the allele frequency being higher in population subgroups in which disease frequency is also higher (population admixture). Diseases with a complex genetic origin, such as asthma, also may be characterized by pleiotropy (the same genotype has different phenotypes), genetic heterogeneity (the same phenotype results from different polymorphisms), and incomplete penetrance (the same polymorphism does not always produce the same phenotype).

Multiple regions of the human genome likely to contain susceptibility genes for asthma and associated phenotypes have been reported from candidate-gene approaches and genome-wide screening studies (52–54). For a candidate gene to potentially be important in the disease, a number of criteria must be met. First, the gene protein product must be relevant to the pathophysiology of the disease. Second, the gene must contain mutations within either the coding region or the regulatory regions controlling gene expression; these mutations need to be functionally relevant. Demonstration of functional relevance for a mutation is particularly important given the high rate of polymorphic variation within the human genome, estimated to be about 1 in 1,000 base pairs in coding DNA and about 1 in 500 base pairs in noncoding DNA. Third, functionally relevant mutations should demonstrate association and/or linkage with an appropriate phenotype. Finally, for a mutation to contribute to disease risk in a population, it must be relatively common: rare mutations may greatly increase the risk of developing asthma in individual families but are unlikely to be important in determining the population risk as a whole. However, it follows that the effects of common polymorphisms may be relatively small; if major deleterious consequences occurred in persons with a given polymorphism, it would soon be lost from the population.

Genes for allergic sensitization

Interleukin (IL)-4. Genetic variants in the promoter region of the *IL-4* gene (55) have been related to elevated immunoglobulin (Ig)E levels. The polymorphism at –589 involves a C→T substitution in the promoter region on chromosome *5q31*, resulting in increased responsiveness to *IL-4* (e.g., by enhanced IgE production). This locus has been associated with asthma diagnosis in some studies (56, 57). In an Australian population (n = 1,004), Walley and Cookson (57) reported positive associations between the *IL-4* promoter polymorphism and specific IgE to dust mite and clinical symptoms of wheeze but could not duplicate these results in a smaller (n = 183) English population.

IL-13. Polymorphisms within the *IL-13* gene are associated with high IgE levels and with the presence of asthma (58). *IL4-Rα* on chromosome 16 is a shared component of the receptor for both *IL-4* and *IL-13*, and polymorphisms in this gene are also associated with asthma and atopy (59). It is of interest that different asthma-associated traits are associated with individual polymorphisms that affect splicing of *IL4-Rα* (60, 61), illustrating the complexity of mechanisms that may vary the actions of a single gene. Gene-gene interactions rarely have been studied, but recently an interaction between polymorphisms in *IL4-Rα* and *IL-13* was reported to increase the risk of asthma fivefold (62).

Innate immunity is becoming recognized as equally as important as specific immunity in the response to mucosal and skin injury. The innate immune system contains many molecules that recognize signals of infection, such as components of the bacterial wall and methylated bacterial DNA. These molecules also up-regulate the specific immune system and may enhance IgE responses. *CD14* is a receptor for bacterial lipopolysaccharide. Polymorphism in the *CD14*

gene is associated with asthma, perhaps providing some of the structural explanation for the hygiene hypothesis (63). This receptor may be part of the signaling mechanisms that mediate the proposed protective effects of childhood infections on asthma development.

Genes for inflammation and tissue damage

Tumor necrosis factor. Tumor necrosis factor (TNF) is an inflammatory cytokine found in increased concentrations in asthmatic airways (64) and in lavage fluid from asthmatic lungs (65). The TNF and lymphotoxin α and β genes are within the human major histocompatibility complex on chromosome *6p* (66, 67). Constitutional variation in the level of secretion of TNF by peripheral blood lymphocytes or monocytes has been established in association with polymorphism in the TNF gene cluster and the *HLA-DRB1* locus (68–70).

Polymorphisms in the TNF genes have been associated with the presence of asthma (71). These polymorphisms act by enhancing the inflammatory process rather than modifying the IgE-mediated allergic response.

The high-affinity receptor for IgE (Fc∈RI) is the central trigger of the atopic response (64). It is multimeric, made up of one alpha, one beta, and two gamma chains. The receptor is also found in an alpha/gamma2 form. The alpha chain binds IgE, and the gamma chains carry out intracellular signaling. The beta chain is not necessary for receptor function but acts as an amplifying element.

Fc∈RI molecules are found on the surface of mast cells in the skin and mucosal lining of the airways and intestinal tract, and on basophils. The receptor binds circulating IgE molecules and holds them at the cell surface. The presence of antigens results in binding and cross-linking of IgE molecules. The resulting aggregation of receptors induces multiple signaling pathways that control diverse effector responses. These responses include secretion of allergic mediators and induction of cytokine gene expression, resulting in release of molecules such as *IL-4*, *IL-6*, TNF-α, and granulocyte-macrophage colony-stimulating factor. These responses are central to the induction and maintenance of allergic inflammation and may confer physiologic protection in parasite infections (64). Fc∈RI also is present on antigen-presenting cells, such as dendritic cells, and participates in IgE-mediated antigen presentation and processing (72).

Genes for asthma severity and bronchial hyperreactivity

Fc∈RI. The β chain of the high-affinity receptor for IgE (Fc∈RI) acts as an approximately sevenfold amplifying element of the receptor response to activation (65). Polymorphism within the chain has been associated with asthma (73), allergy (74), bronchial hyperresponsiveness (75), and atopic dermatitis (76). These variations seem to be associated with severe atopic disease.

IL-4. Genetic markers within and around chromosome *5q31-33* have been linked to total serum IgE concentration in the United States (77) and Holland (78, 79). These markers provide strong evidence of one or more loci in *5q31-33* closely involved in raised serum IgE levels and bronchial hyperresponsiveness. The gene encoding *IL-4* is within this region and is a possible candidate for the reported genetic linkage.

Because *IL-4* stimulation can influence mast cell responsiveness to IgE-mediated signaling, and because genetic variants in *IL-4* can modify *IL-4* gene transcription, these sequences also may modify asthma severity. In a study of 772 White and African-American asthmatics, the presence of the mutant *IL-4* promoter allele was associated with forced expiratory volume in 1 second of less than 50 percent among White study subjects. In Japan, polymorphisms of the *Ile50* allele of the *IL-4* receptor gene were associated with increased moderate-to-severe atopic asthma, especially in infants with onset within 2 years of age (80). Fatal and near-fatal asthma and severe airflow obstruction have been associated with polymorphisms in the *IL-4 589T* and *IL-4 RA576R* alleles, respectively (81).

IL-13. The Th2 cytokines *IL-4* and *IL-13* have a critical role in IgE synthesis. *IL-13* is closely related to *IL-4*, and the two genes arose from duplication of a single precursor. The receptors for both cytokines share an alpha chain (*IL-4Rα*), which, when knocked out, greatly reduces IgE production (82). *IL-13* appears to affect asthmatic airways beyond simply enhancing IgE production (83).

β_2 Adrenergic receptor gene. Another candidate gene mapped to chromosome *5q* is the β_2 *adrenergic receptor* (*AR*) gene. Several lines of evidence from experimental asthma have suggested that β_2-*AR* may be related to asthma (84, 85). Two common polymorphisms of this gene at codons 16 and 27, *Arg16-Gly* and *Gln27-Glu*, were present with high allelic frequencies in both asthmatic and normal populations (86). Results from in vitro β_2-*AR* experiments, using Chinese hamster fibroblast cells transfected with human airway smooth-muscle cells in tissue culture, suggested that these two polymorphisms are involved in agonist-promoted receptor down-regulation (87, 88). A substitution of arginine for glycine at codon 16 resulted in increased down-regulation of β_2-*AR* after agonist challenge. In contrast, a substitution glutamic acid for glutamine at codon 27 conferred attenuated down-regulation. However, results from several small clinical studies were inconsistent, in part because these two polymorphisms were common and in linkage disequilibrium. The polymorphism at codon 16 was reported to be associated with asthma severity, nocturnal asthma, and airway hyperresponsiveness (86, 89, 90) but not with fatal or near-fatal asthma (91). On the contrary, Hall et al. (92) reported that *Gln27-Glu* was associated with *lower* airway reactivity in subjects with mild-to-moderate asthma.

ADAM-33. The *ADAM-33* gene has recently been shown to be expressed by lung fibroblasts and bronchial smooth muscle cells (93), and it has been suggested that polymorphisms may influence smooth muscle cell and fibroblast proliferation, possibly leading to increased inflammation (94). Further work is needed to confirm the precise role of *ADAM-33* in asthma development.

PERINATAL RISK FACTORS

The greater influence of maternal compared with paternal asthma and atopy on the development of asthma in offspring suggests a role of the perinatal environment. In this section, we first review environmental risk factors occurring during the intrauterine period, which is often neglected even in studies that follow up children from birth. Factors that influence asthma development through allergic sensitization of the fetus or through alteration of the fetal environment are considered. Next, factors occurring in the neonatal period, including diet and lactation, and the nursery environment, are reviewed. Finally, we comment on environmental risk factors in early childhood.

Intrauterine risk factors for atopy and asthma development

Despite a large literature on risk factors for the development of asthma in children, almost nothing is known about the role of intrauterine factors (95). Aspects of the fetal environment that have been implicated in asthma development in the offspring include in utero immune responses and inadequate oxygenation and lung maturation.

Allergic sensitization in the fetus. Atopy is one of the most important risk factors for developing asthma, and nearly all asthmatics have altered immune responses (96). The human immune response begins in utero, and gestation and early childhood are thought to be the most influential periods with regard to atopic expression (97). Exposure to allergens begins during the perinatal period. The human fetus appears to produce IgE, but at relatively low levels. Nonetheless, higher total IgE levels in cord blood (>0.8 kU/liter) have been observed and were associated with increased risk for atopic disease in infancy, including atopic dermatitis (98, 99), and urticaria from food allergy (100), but the majority of studies have found little predictive value of cord blood IgE on asthma or asthmatic symptoms (98–107) because of the low sensitivity and predictive value of IgE (98, 102, 107–109). However, none of the studies of the predictive value of cord blood IgE has been conducted among subjects with any substantial understanding of their genetic polymorphisms, examples of which have just been described, or a detailed examination of their residential aeroallergen exposure, reviewed below.

It is widely assumed that maternal IgE does not cross the placenta (110), although IgG does (111), and that increased cord blood IgE may be due to intrauterine sensitization. Neonatal sensitivity to cow's milk, penicillin, helminthes, and grass pollen has been observed (112–118). Alternatively, elevated neonatal IgE may be due to nonspecific spontaneous IgE synthesis or to transplacental transfer of maternal IgE antibodies to cord blood that promotes fetal antibody formation (95). It has been shown that cord blood lymphocytes are stimulated by food and inhaled allergens (119, 120) but not known is whether this is a "sensitization" response, which predisposes the neonate to an allergic response, or normal immune system maturation (95). In one recent study of children with a family history of asthma, elevated IgE levels at 6 months of age did predict asthma in the children at age 6 years (121).

Maternal transfer of IgG antibodies to the fetus confers immunity to some infectious diseases (111). Protection against other infectious diseases may itself lower atopy and asthma risk, since infections can alter mucosal barriers and influence immune responses (95). Maternal vaginitis and febrile infection during pregnancy was shown to increase asthma risk in offspring at age 7 years (122), as did infection of the amniotic cavity (123). It is also possible that maternal IgG response to some foods may protect infants from sensitization, but this possibility remains controversial (124–128). Vassella et al. (129) observed that elevated cord blood IgE and IgG were associated with fewer allergies during the first 18 months, particularly in infants with a family history of allergy.

Induction of neonatal IgE and IgG antibodies as a result of changing the maternal diet has been the subject of intervention trials (130, 131). Cow's milk, egg protein, fish, and peanuts were excluded from the maternal diet, whereas, in other studies, maternal milk and egg consumption were increased to stimulate IgG antibody development; however, neither strategy appeared successful (132). Because these trials examined only a main effect of diet, they do not inform us of any role that maternal Ig status owing to diet may have on infant allergy when considered in combination with other genetic and environmental risk factors.

A recent trial influenced the fetal environment of 132 high-risk infants; their mothers were randomly given the oral probiotic *Lactobacillus* GG during the later stages of pregnancy, and the newborns directly received the probiotic through breast milk after delivery (133). At age 2 years, children given the probiotic had half the rate of atopic eczema of the placebo group (23 percent vs. 46 percent, $p = 0.008$). Overall, six children developed asthma, who were not meaningfully distinguished by their probiotic therapy.

Influences of the fetal environment. An adequate fetal environment is critical to the growth and development of the fetus. Inadequate oxygenation and/or nutrition can lead to disruption of lung maturation. If early or severe enough, irreversible pulmonary abnormalities may persist (134). Maternal smoking during pregnancy is indisputably linked to fetal growth retardation, and passive smoke exposure may have similar effects (135–137). Maternal smoking also appears to increase the risk of asthma in the infant (138–144), although it has been difficult to disentangle the intrauterine risk from the effects of passive neonatal exposure (145). Recent work suggests that in utero exposure to maternal smoking without postpartum exposure to environmental tobacco smoke increases the risk of a child having physician-diagnosed asthma, although exposure to environmental tobacco smoke during childhood was related to wheeze but not asthma (146).

In addition to presumably conferring a genetic risk, maternal asthma, a condition associated with impaired respiratory function and possibly decreased oxygenation of the fetus, also may affect asthma development in offspring by affecting fetal development. This may explain why, in the genetic studies, maternal asthma confers more risk than paternal asthma (41, 42). Asthmatic status during pregnancy

has been linked in some studies but not others to poor birth outcomes. Results are equivocal regarding gestational diabetes (123, 147, 148), preterm labor (123, 147, 149–152), preterm delivery (147, 148, 150–154), fetal growth (155–157), and low birth weight (147, 156–161). A consistent, increased risk of hypertension during pregnancy among asthmatics has been found in prior research (123, 147, 148, 151, 153, 154, 156). Recently, umbilical artery flow velocity from Doppler ultrasound was found to be significantly reduced at 18 weeks' gestation in moderately and severely asthmatic mothers (162). Intrauterine exposure to beta agonists (163) and poorly managed maternal asthma (164, 165) have been associated with asthma development in children, but the independent effects of each have not been disentangled. These risk factors may contribute significantly to the burden of asthma, because 3.7–8.4 percent of US pregnancies have been estimated to be affected by maternal asthma (166).

Perinatal outcomes that indicate a compromise in the fetal environment have been inconclusively linked to asthma development. Preterm delivery has been shown to be possibly associated with asthma development in children (156, 167, 168), as has low birth weight (169–171). Very-low-birth-weight infants (<1,500 g) rarely have been studied, but, in one study, risks of asthma appeared to be associated with very low birth weight itself but not with other perinatal factors (172).

One Norwegian study tried to distinguish between maternal obstetric conditions (hyperemesis, hypertension, and preeclampsia) and uterine factors (antepartum hemorrhage, preterm contractions, placental insufficiency, and uterine growth restriction) and found an association only with the latter group for asthma at age 4 years. These results were observed in both atopic and nonatopic parents. IgE status of the children at birth was not recorded (173). In a recent Finnish study, risk of atopy until 31 years of age increased linearly with increasing gestational age from 35 weeks on, particularly among children of farmers, although farmers' children overall were at lower risk of atopy (174). We speculate that children born preterm and with immature immune systems react differently to allergens and antigens than do infants born later. In the Finnish study, no relations were observed between risk of atopy and asthma, indicating the complex etiology of that disease and the importance of also studying the genotype. The role of mother's education (11, 15, 18) and family income (15, 16, 22), which are associated with negative perinatal outcomes and increased asthma in children, also needs to be addressed in future studies.

Other perinatal factors implicated as possible risk factors for atopic disease and asthma development include increased ponderal index and decreasing maternal age (175), stress during pregnancy (176), delivery by cesarean section (177), hypertensive disorders of pregnancy and gestational diabetes (123), use of prostaglandins and hormones during pregnancy (178), breech and instrumental delivery (179), and early or threatened labor and malpresentation of the fetus (180). Male gender (2, 15, 16, 18, 181) is a well-recognized risk factor. Having older siblings was protective for asthma diagnosed after age 2 years in one recent study but was a risk factor for earlier diagnosis (182), also pointing to the importance of deconstructing the risk factors for intrauterine, early neonatal, and later infancy exposure.

The influence of lactation and diet

The role of lactation in infant atopy and asthma remains controversial. Studies have reported protective effects of breastfeeding on asthma (183–185) and recurrent wheeze (16, 186, 187), increased risk of asthma related to breastfeeding (186, 188–190), and no relation between the two (16, 191, 192). Methodological issues in these studies include differences in defining breastfeeding, in study populations, and in age of the child when the outcome is assessed.

Breastfeeding has been variously defined as any versus none (16, 183, 187, 191), by duration (185, 186, 188), or as exclusive breastfeeding versus combined with formula or solid food (184, 189, 190, 192). None of these definitions consistently has been related to asthma outcome. For example, Oddy et al. reported that exclusive breastfeeding for 4 months or more was protective against asthma development (184). Takemura et al. reported a small increased risk of asthma among children exclusively breastfed (190). Wright et al. described a threefold increased risk of asthma among atopic children who were exclusively breastfed for 4 months or more and whose mothers had asthma (189). In another study, Wilson et al. reported that introduction of solid food before age 4 months increased the risk of wheeze, but exclusive breastfeeding was unrelated to asthma diagnosis (192).

Similarly, different study populations have provided quite different answers to the question of whether breastfeeding influences asthma development. Studies of population-based samples have yielded protective effects (183, 185), have suggested increased risk (188, 190), and have found no association (16, 192). Areas in which the prevalence of asthma is high have been found to have both a protective association of breastfeeding in Australia (184) and an increased risk in New Zealand (188), while a study of atopic families found no association (191).

There is somewhat more consistency when the literature is examined according to age of the child. Studies of young children (to age 6 years) often have reported that breastfeeding reduces the risk of asthma (183–185), while studies of older children (190) and young adults (188) are more likely to report that breastfeeding increases risk. In a large Italian study (186), breastfeeding for 6 months or more reduced the risk of wheeze in the first 2 years of life but increased the risk of late-onset wheeze. The Tucson Respiratory Study reported that breastfeeding prevented asthma when children were assessed at age 6 years (187), but breastfeeding increased the risk of asthma at age 13 years (189) among children whose mothers were asthmatic.

Any protective effect of lactation may be influenced by the mother's own immune status. Factors that suppress IgE have been reported in colostrum, the first-expressed breast milk (193). A randomized trial to compare cow's milk with banked human milk in preterm infants reported greater allergic disease in the infants exposed to cow's milk by 18 months of age (194). It is possible that exposure to some

food allergens in breast milk increases IgE sensitization (195) and that breast milk itself may increase milk-specific IgE (196), perhaps from the mother's own diet of cow's milk. Thus, maternal diet is an important factor when considering the effect of lactation on atopy (197).

Trials of both maternal and infant avoidance of allergenic foods have indicated a lower risk of food allergies but not asthma in the intervention group (130, 198). Only one trial has been known to combine food allergen avoidance with dust mite restriction, and, while reduced asthma and atopy were observed at 1 year of age (199), the effect was diminished at age 2 years (200). None of the trials of food avoidance considered gene-environment interactions; new trials should consider genetic susceptibility as an effect modifier.

Early neonatal risk factors

It recently was observed that, after adjustment for several potentially confounding factors, newborns who spent their first night in a communal nursery were at increased risk of developing hay fever (odds ratio = 1.48, 95 percent confidence interval: 1.23, 1.77) (201). The authors speculated that infants in the nursery were more likely to experience low-dose and short-duration exposure to nonfamilial microorganisms. This study was conducted in a 1970 birth cohort, and the care of newborns is very different today, particularly with the greater use of neonatal intensive care nurseries. However, these nurseries can themselves expose infants to a range of microorganisms that may be important for sensitization to asthma or to protection against future asthma (202). It also is known that the early extrauterine environment of the infant's immune system is dependent on gut microflora through lipopolysaccharides in Gram-negative bacteria and that different bacteria induce various cytokines (203, 204). This knowledge raises the possibility that use of antibiotics in the neonatal nursery may enhance the future development of asthma. Older children treated with antibiotics have shown increased rates of asthma (205). Antibiotic use in early infancy has been observed to strongly increase risk of asthma at ages 5–10 years (odds ratio = 4.0, 95 percent confidence interval: 1.6, 10.6) (206). These findings also raise hypotheses about the use of antibiotics in the newborn intensive care nursery as well as obstetric antibiotic use, although confounding by disease indication in future studies will require careful control.

It has been observed that babies born preterm, of low birth weight, and needing positive pressure ventilation at birth, as well as having mothers who smoked during pregnancy, have an increased susceptibility to asthma (207–209). Babies with low 1- and 5-minute Apgar scores are also at increased risk (179), but all of these factors are more common in those who have spent time in the neonatal intensive care nursery. Consequently, the independent effects of antenatal versus early postnatal exposures have not been satisfactorily delineated, perhaps because, to our knowledge, they have never been studied in the same cohort.

Environmental risk factors in infancy and early childhood

Allergens in house dust have been controversially implicated in the development and severity of asthma in children. House dust mite (210–216), cat (217–222), dog (223–225), cockroach (218, 226–229), and fungi (211, 213–216, 230–234) allergens are among the most important because of their suspected role in the development and exacerbation of asthma. Recent cohort studies that measured allergen exposure in infancy and followed children for recurrent wheeze and asthma have failed to find a strong association with dust mite or cat allergen (191, 235–237). One study that stratified by maternal asthma status suggested an interaction between exposure and genetic susceptibility (237).

At least three studies (35, 238, 239) found an association between mold in homes and respiratory symptoms. Recent studies have reported that house dust endotoxins independently increased symptoms of wheeze in the first year of life (240), and in utero allergen sensitization is common and may involve *IL-5* regulation (241). Endotoxin, a lipopolysaccharide from the outside layer of Gram-negative bacteria found in the fecal material of large mammals, is of particular interest for the hygiene hypothesis. This hypothesis followed observations that children reared on farms had lower rates of asthma than did children from urban environments (242). A recent publication (243) found that endotoxin levels from the mattresses of children aged 6–13 years in rural European communities, but not necessarily from farms, were inversely related to atopic asthma and hay fever as well as to cytokine production by leukocytes, indicating increased tolerance of exposure to endotoxin and other allergens.

A particularly important indoor air contaminant in the exacerbation of asthma, environmental tobacco smoke, is associated with a wide range of acute and chronic effects (142, 244–246.) The US Environmental Protection Agency calculated that the children of mothers who smoked 10 or more cigarettes daily had a 90–600 percent increased risk of developing asthma and that 48–83 percent of all cases of asthma in the children of these women could be attributed to their mother's smoking (247). A recent California study reported that maternal smoking primarily increased the risk of early-onset persistent asthma, particularly in children with a history of parental asthma, suggesting the importance of further defining the genotype of at-risk children (248).

Limited human and animal data suggest that air contaminants, particularly ozone and nitrogen dioxide, may modulate immune responses to inhaled biologicals (139, 199, 249, 250). Viral (251–253) and respiratory (44, 254, 255) infections before the age of 2 years have been associated with increased risk of asthma. Indoor heating sources (34, 256), use of gas stoves (34, 257, 258), and nitrogen dioxide exposure (258–263) have all been related to increased infant respiratory symptoms.

SUMMARY AND THEORETICAL MODEL

Asthma development and severity are almost certainly influenced by a multifactorial etiology that includes genetic, immunologic, and environmental factors. Many of these risk

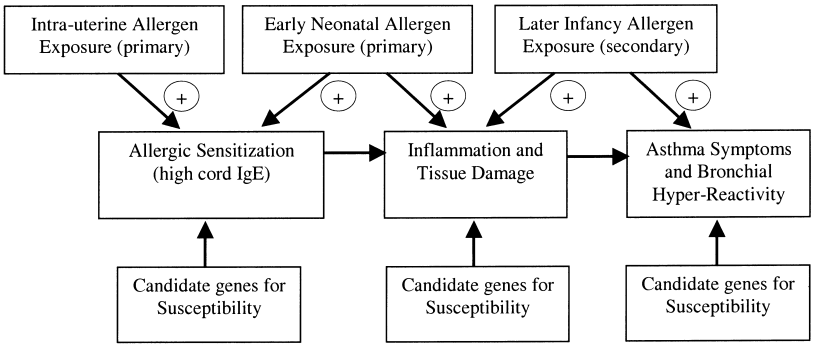

FIGURE 1. Hypothesized associations of genetic, intrauterine, and perinatal risk factors with asthma onset and severity in infancy, modified from Wahn (267). Ig, immunoglobulin.

factors may start to exert their effect during intrauterine life (264–266). Future research, by building on these risk factors and a detailed investigation of the mother's own asthma status during the index pregnancy, may start to shed some light on these relations.

No single factor is likely to be responsible for the observed increase in asthma onset and severity, particularly the increase in minority populations. It is almost certainly due to new environmental factors, since the gene pool is unlikely to have changed meaningfully in the last 20–30 years. New environmental factors will influence phenotypes genetically susceptible to them, at selected stages in the development of disease. We have suggested that asthma development may start as early as the fetal period and is certainly well established during infancy.

The hypothetical roles of the major groups of risk factors, discussed throughout this review, are shown in figure 1, which has been modified from Wahn (267) to emphasize the role of intrauterine and early neonatal exposures. It is likely that a complex interplay of these factors is responsible for asthma development and severity. Current knowledge suggests that development of asthma requires polymorphisms in several genes in the same person, which will lead to complex gene-gene and gene-environment interactions. These interactions are likely to come into play at different stages during early life, as the child becomes exposed to a variety of environmental insults. These complex interactions make it difficult to initially identify candidate genes and, once identified, to understand the full role they play in asthma development and severity.

Although a number of susceptibility genes for asthma have been identified, it is almost certain that the majority remain to be described. Analysis of shared haplotypes (linear arrangements of alleles on a chromosome) of affected persons from "founder populations" with a common ancestor is increasingly being used to identify candidate asthma genes (268). Furthermore, with publication of the human genome, candidate asthma genes are likely to be identified at an increasing rate. The expected plethora of candidate genes will pose problems of its own unless fundamental epidemiologic principles are followed. These principles include the need for replicating findings in alternative populations, considering publication bias in the evolving literature, systematically reviewing evidence for a candidate gene, and conducting a meta-analysis of its effects when appropriate. Application of other criteria for causality, well known to epidemiologists, will be important. Included are strong associations unconfounded by population stratification, biologic plausibility (what is the function of the gene's protein products?), and dose response based on homo- or heterozygosity. To organize this complex body of data into testable hypotheses, increasingly sophisticated theoretical modeling of new associations will be required.

Although exposure to perinatal factors, allergens, and other environmental risk factors increases the risk of asthma, only a portion of exposed neonates will develop asthma. We conclude that neonates' susceptibility will vary based on their genetic and immunologic predisposition, and identification of at-risk genotypes will permit more precise specification of environmental risk models. Study cohorts are required in which both parents and the index child can be genotyped and the child prospectively followed from *early pregnancy* through infancy. These studies will enable analysis of the gene-gene and gene-immunologic-environment interactions likely to fundamentally influence asthma onset and severity. Our model has utility in considering the interplay of the genotype with environmental factors, because it points to the focus of clinical specialists: obstetricians, perinatologists, and pediatricians. In the future, the management of patients is likely to be influenced by pharmacogenetic studies of the responsiveness of patients with selected polymorphisms to a particular medication. The model also emphasizes the need for continuity of care among patients at risk of asthma and the importance of understanding the complex nature of asthma etiology if more effective prevention programs are to be launched. Knowing the genetic risk of patients may permit more targeted allergen avoidance strategies (269).

The model is also overly simple. A particular polymorphism may influence the course of asthma at more than one stage. As described earlier, *IL-13* polymorphisms have already been shown to increase the risk of atopy and asthma severity. At the same time, environmental interactions are becoming more apparent. Babies born preterm and also

exposed to environmental tobacco smoke are at an enhanced risk of asthma. There are extremely difficult technical problems, which are outside the scope of this review, in designing studies able to identify gene-gene-environment-environment interactions, and we are aware of none conducted to date for any disease. However, asthma is a disease for which such a complex array of factors will almost certainly be needed to explain substantial amounts of variance in asthma risk.

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